

Europäisches Patentamt
European Patent Office
Office européen des brevets



(11) **EP 1 145 735 A2**

(12) **EUROPEAN PATENT APPLICATION**

(43) Date of publication:
17.10.2001 Bulletin 2001/42

(51) Int Cl.7: **A61N 1/36**

(21) Application number: **01303245.3**

(22) Date of filing: **05.04.2001**

(84) Designated Contracting States:
**AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU
MC NL PT SE TR**
Designated Extension States:
AL LT LV MK RO SI

(72) Inventor: **Pless, Benjamin D.**
Atherton, California 94027 (US)

(74) Representative: **Price, Nigel John King**
J.A. KEMP & CO.
14 South Square
Gray's Inn
London WC1R 5JJ (GB)

(30) Priority: **05.04.2000 US 543264**

(71) Applicant: **Neuropace, Inc.**
Sunnyvale, CA 94085 (US)

(54) **Neurostimulator involving stimulation strategies**

(57) This is a neurostimulator that is configured to treat epilepsy and other neurological disorders using certain stimulation strategies, particularly changing var-

ious pulse parameters, during the imposition of a burst of those pulses. The invention includes the processes embodying those stimulation strategies.

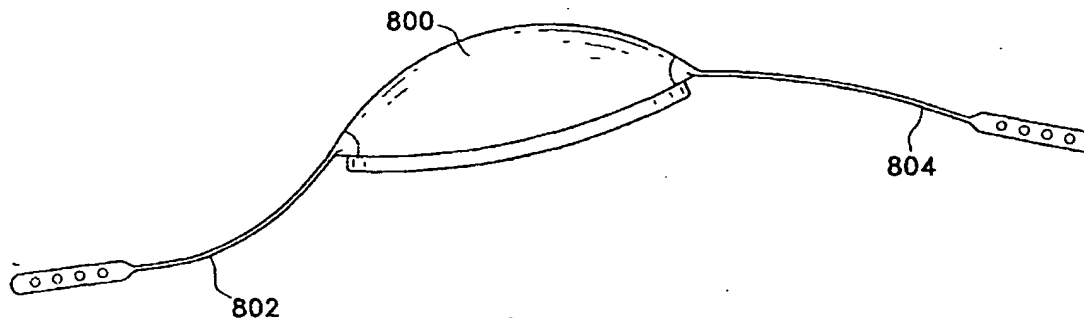


Fig. 8

EP 1 145 735 A2

Description**Field of the Invention**

5 [0001] This invention is to a neurostimulator, preferably implantable in the cranium, that is configured to treat epilepsy and other neurological disorders using certain stimulation strategies, particularly changing various pulse parameters during the imposition of a burst of those pulses. The invention also includes processes embodying those stimulation strategies.

Background of the Invention

10 [0002] Epileptic seizures are characterized by excessive or abnormally synchronous neuronal activity. Neurologists recognize a wide variety of seizures. Partial onset seizures begin in one part of the brain; general onset seizures arise throughout the entire brain simultaneously. When partial onset seizures progress to involve much of the brain, they are said to have "secondarily generalized." Some seizures result in the loss of conscious awareness and are termed "complex" seizures. So-called "simple" seizures may involve other symptoms, but consciousness is unimpaired. Seizure symptoms may include sensory distortions, involuntary movements, or loss of muscle tone. The behavioral features of a seizure often reflect a function of the cortex where the abnormal electrical activity is found.

20 [0003] Physicians have been able to treat epilepsy by resecting certain brain areas by surgery and by medication. Brain surgery is irreversible, and is ineffective or is associated with neural morbidity in a sizable percentage of cases. Medication is the most prevalent treatment for epilepsy. It is effective in over half of patients, but in the remainder of the patients, the medication is either ineffective in controlling seizures, or the patients suffer from debilitating side effects. A more promising method of treating patients having epileptic seizures is by electrical stimulation of the brain.

25 [0004] Since the early 1970's, electrical brain stimulators have been used which provide more or less constant stimulation, the stimulation largely being unrelated to detected electrical activity.

30 [0005] Electrical stimulation of the nervous system has been used to suppress seizures. A device is described in Cooper et al. for stimulation of the cerebellum. See, "The Effect of Chronic Stimulation of Cerebellar Cortex on Epilepsy and Man," I.S. Cooper et al in *The Cerebellum, Epilepsy and Behavior*, Cooper, Riklan and Snyder Edition, Plenum Press, New York 1974. Others have utilized devices which stimulated the centro median nucleus of the thalamus. See, "Electrical Stimulation of the Centro Median Thalamic Nucleus in Control of Seizures: Long Term Studies." F. Valasco et al, *Epilepsia*, 36 (1): 63-71, 1995. Chaos Theory has been used to apply stimulation to a seizure focus *in vitro* to abort the seizure. See, S. Schiff et al, "Controlling Chaos in the Brain," *Nature*, Volume 370, August 25, 1994.

[0006] As described in patent 6,016,449, an improved brain stimulator is implanted in the cranium and has leads terminating with electrodes in contact with brain tissue.

35 [0007] Conventional neurostimulators use fixed rate trains of either monophasic or biphasic electrical pulses of a fixed amplitude to stimulate neural tissue (ref?). Neurons in the immediate vicinity of the electrodes are induced to fire (i.e. are recruited) by the electrical pulses thereby modifying the natural electrical activity in the brain. During an epileptic event, there is abnormal synchronization of neural activity in the brain. The present invention improves upon the prior art by varying the timing, amplitude and/or duration of the pulses to more effectively disrupt the synchronized activity. Furthermore, the subject invention analyzes the effect on the brain of the electrical pulses, and decides how to modify the burst parameters in a subsequent burst to most effectively terminate the seizure.

40 [0008] Responsive stimulation, specifically electrical stimulation, that is applied to the brain, has not yet been used to treat patients in long-term studies. This is true even though there are algorithms suitable for detection of the onset of an epileptic seizure. For instance, Qu et al provide an algorithm said to recognize patterns of electrical activity similar to those developed while recording an actual epileptic seizure. See, Qu et al., "A Seizure Warning System for Long-Term Epilepsy Monitoring," *Neurology*, 1995; 45:2250-2254. Similarly, Osario, et al. have suggested an algorithm applied to signals from intracranial electrodes with good results. See Osario, et al. "A Method For Accurate Automated Real-Time Seizure Detection," *Epilepsia*, Vol. 35, supplement 4, 1995.

50 [0009] As used herein, "epileptiform activity" refers to the manifestation on an EEG (cortical, depth, or scalp) of abnormal brain activity whether associated with clinical manifestations or not. "Stimulation" or "electrical stimulation" means the application of an electric field or electric current to biological tissue.

[0010] The inventive device and related process:

1. have improved ability to terminate epileptiform activity.
2. are less likely to initiate epileptiform activity if stimulation is accidentally delivered during a normal EEG.
3. are less likely to generalize ongoing epileptiform activity.
4. are safer since the current density required to affect a larger amount of brain tissue is lower than that found in the prior art.

[0011] None of the cited documents describes the inventive procedures and devices described below.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012]

Figure 1A shows constant pulse-to-pulse intervals in prior art burst.
 Figures 1B to 1E depict varying pulse-to-pulse intervals for a burst according to the inventive process.
 Figure 2A shows a prior art burst having a constant pulse amplitude.
 Figures 2B and 2C depict varying pulse amplitudes for a burst according to the inventive process.
 Figure 3A shows a typical prior art pulse.
 Figure 3B shows a pulse with a hyperpolarizing prepulse.
 Figure 4A shows a prior art burst having constant pulse widths.
 Figures 4B and 4C depict varying pulse widths for a burst according to the inventive process.
 Figures 5A, 5B, and 5C depict epileptiform activity in the brain.
 Figure 6 depicts variously a representative EEG of epileptiform activity and a selection of burst initiations done according to the invention that represent various stages of delay from peaks detected as shown in Figs. 5A-5C.
 Fig. 6A shows a multiple brain electrode in conjunction with an epileptogenic focus.
 Figures 7A to 7E depict examples of bursts with varying pulse parameters as might be applied to the Figure 7A device.
 Figure 8 is a depiction of one variation of the inventive neurostimulator having multiple electrodes.

DETAILED DESCRIPTION OF THE INVENTION

[0013] This invention recognizes the phenomenon that stimulation which precipitates epileptiform activity is promoting synchronized activity in the brain; stimulation intended to terminate epileptiform activity desynchronizes brain activity. Therefore different parameters for stimulation are better depending upon whether the burst is intended to provoke or terminate seizures.

[0014] This invention uses various parameters to optimize stimulation to desynchronize the brain activity to terminate epileptiform activity:

Pulse-to-Pulse Interval Variation

[0015] In one variation for treating epilepsy, the pulse-to-pulse interval within a burst is not fixed as in prior art devices. To better desynchronize neuronal activity, the pulse-to-pulse interval is varied as shown in Figure 1. The pulse-to-pulse intervals are generally kept to a range of 3 to 300 msec, and may be varied randomly or changed in a systematic fashion, such as incrementing or decrementing the pulse to pulse interval within a burst. In addition to providing a better modality for terminating epileptiform activity, a burst with a varying pulse-to-pulse interval can be optimized to avoid inducing epileptiform activity, or generalizing a local seizure while maintaining high efficacy in terminating seizures. Once the electrodes are placed near the epileptogenic focus in the brain, the physician can use bursts of pulses both to initiate and to terminate epileptiform activity. By varying the burst parameters, it is possible to arrive at a parameter set that is effective at terminating epileptiform activity, but is ineffective at initiating it. For the purposes of this patent, a burst may be any number of pulses, typically in the range from 1 to 100.

[0016] The examples shown in Figures 1A to 1E depict burst durations of approximately 400 msec for illustrative purposes. Burst durations of 10 msec to 2000 msec or even longer may all be effective in terminating epileptiform activity. Figure 1A shows a prior art fixed rate burst with the pulse-to-pulse interval fixed at 20 msec. Figure 1B shows a representative burst where the pulse-to-pulse interval is varied in a random, pseudo-random, or fractal fashion within the burst. Figure 1C shows a burst where the pulse-to-pulse interval decrements within the burst. Figure 1D shows a burst where the pulse-to-pulse interval first decrements and then increments within the burst. Figure 1E shows a burst that is made up of shorter bursts. In the variation shown in Figure 1E, the pulse sequence within the shorter bursts, the shorter burst durations, and the intervals between the shorter bursts may be varied as described with respect to Figures 1B to 1D. Additional burst patterns may be generated from the basic patterns described herein without departing from the scope of this invention.

Pulse Amplitude Variation

[0017] Another inventive method for desynchronizing brain activity and terminating epileptiform activity is by spatially desynchronizing activity in the vicinity of the stimulation electrode. To accomplish this, various individual pulse param-

eters within a burst are varied for at least a portion of the burst. Specifically, by varying the amplitude of the pulses, individual pulses may be tailored to directly depolarize different neural tissue. Lower amplitude pulses directly depolarize tissue in the immediate vicinity of the electrode; higher amplitude pulses directly depolarize tissue both near the electrode and at some distance from the electrode. By varying the amplitude of the pulses within a burst, local tissue is depolarized at a higher rate than tissue somewhat distant from the electrode. The spatial heterogeneity of the timing of depolarization around the electrode is more effective in desynchronizing brain activity than prior art pulse regimes. [0018] In Figure 2A to 2C, the fixed rate bursts are depicted with durations of approximately 400 msec for illustrative purposes only. Figure 2A shows an example of a prior art, fixed amplitude burst. Figure 2B shows a burst having a systematic variation of pulse amplitude within the burst. Figure 2C shows a burst where the pulse amplitude within the burst varies in a random, pseudo-random, or fractal fashion.

Hyperpolarizing Prepulse

[0019] A variation of the inventive technique is to include a hyperpolarizing prepulse to render tissue near the electrode less sensitive than tissue at some distance from the electrode. This allows more independent control of the sequence of depolarization of tissue near and more distal to the electrode. Figure 3A shows a typical prior art pulse having a stimulating phase 301 and a charge balance phase 302 of equal duration. Typical phase durations vary from 40 to 500 microseconds. Figure 3B shows a pulse having a hyperpolarizing prephase 303 followed by a stimulating phase 304. The prephase 303 is typically of low amplitude and longer duration, and would not stimulate tissue effectively if used on its own. The stimulating phase 304 is of higher amplitude and its duration may be adjusted to charge balance the hyperpolarizing prephase 304. The pulse described in Figure 3B maybe used selectively or throughout the stimulation strategies discussed in conjunction with the inventive variations found above.

Pulse Width Variation

[0020] In addition to varying the pulse amplitude, it is advantageous also to vary the pulse width of individual pulses within a burst. Shorter pulses (on the order of 50 to 150 microseconds) tend to directly depolarize smaller diameter nerve cells. Longer pulses (100 to 500 microseconds) depolarize larger diameter nerve cells. By varying the pulse width of the pulses within a burst, it is possible to preferentially depolarize larger nerves with some of the pulses and smaller nerves with other pulses. The result is a greater spatial variation of the distribution of stimulated nerves on a pulse by pulse basis which results in greater efficacy in desynchronizing brain activity thereby terminating epileptiform activity.

[0021] In Figures 4A to 4C, the number of pulses within the bursts is fewer than in previous examples, and the width of the pulses within the bursts is exaggerated for clarity. Figure 4A shows a typical prior art burst where the pulse widths of the pulses within the burst are all the same. Figure 4B is an example of a burst where the pulse widths are varied in systematic fashion. Figure 4C is an example of a burst where the pulse widths are varied in a random, pseudo-random or fractal fashion.

[0022] Since the tissue disposed near an electrode may have highly variable anatomy, it is anticipated that all of the parameters described above with regard to the Figures (e.g., pulse to pulse interval, pulse amplitude, the use of hyperpolarizing pulses, and pulse width) may be varied alone or in combination to optimize the ability of a burst to terminate epileptiform activity in the brain while improving the safety of the burst by reducing the likelihood of inducing epileptiform activity or generalizing such pre-existing activity.

EEG-based Stimulation - Pulse-to Pulse Interval

[0023] In addition to producing bursts that contain intervals that are set in absolute time increments, this invention provides the improvement of setting pulse-to-pulse interval based upon the detected interval of the epileptiform activity as sensed on the electrodes in contact with the brain. In this mode of operation, the rate of the sensed epileptiform activity is detected and measured. The rate of the detected activity may be used to determine specific pulse-to-pulse intervals or average pulse-to-pulse intervals of the burst used to terminate the epileptiform activity.

[0024] Figure 5A to 5C illustrate a method for generating a burst where some or all of the pulse-to-pulse intervals are based upon the rate of the epileptiform activity. Figures 5A, 5B, and 5C show typical examples of epileptiform activity detected from electrodes in contact with the cortex near the epileptogenic region of a brain. The first step is to determine the rate or average rate of the epileptiform activity. By detecting the peaks of the epileptiform activity, and counting (for example) four intervals, and dividing the result by four, the average interval, I_{avg} , may be determined. Peak detection and interval measurement is well known in the art of automated EEG analysis. See, for instance, "Automatic Detection of Seizures and Spikes" Jean Golman, Journal of Clinical Neurophysiology, 16(2):13-140, 1999 and U.S. Pat Appl. Ser. No. 09/517,797, filed March 2, 2000, entitled "Neurological Event Detection Using Processed

Display Channel Based Algorithms and Devices Incorporating These Procedures", the entirety of which are incorporated by reference.

[0025] Peak markers 501, 503, and 505 in Figures 5A, 5B, and 5C respectively delineate four intervals of each of the epileptiform examples. The measurements X, Y, and Z shown by 502, 504 and 506 in Figures 5A, 5B and 5C respectively are divided by four to give the I_{avg} in each case. It may be desirable to use more or less intervals in calculating the interval average, or the mode or some other mathematical means may be used without departing from the intention of this invention.

[0026] Once the I_{avg} has been determined, it may be used in my inventive process to set pulse-to-pulse intervals within a burst. For example in Figure 1A, the pulse-to-pulse interval in the fixed rate burst may be determined by taking a percentage of the measured I_{avg} . The following table of derived pulse-to-pulse intervals for a burst provides a number of calculated percentages, the use of which will be apparent just below:

Measured I_{avg} (msec)		60	80	120
Percent	10%	6	8	12
	20%	12	16	24
	30%	18	24	36

[0027] As can be seen, for a given programmed setting of percentage, the pulse-to-pulse interval of the burst varies to accommodate different epileptiform waveforms. This provides an advantage over prior art fixed rate intervals in terminating epileptiform activity.

[0028] To apply the same principle to the burst of 1B, the average pulse-to-pulse interval may then be set to be equal to a percentage of the measured I_{avg} . For Fig 1C and 1D, the initial interval may be set equal to or set to a percentage of the measured I_{avg} . Subsequent intervals may then be calculated by adding or subtracting a fixed value or percentage from the previous interval. The pulse-to-pulse intervals shown in Fig 1E may be calculated in the same manner as those of the previous examples.

[0029] The range of percentages used may be from 5% to 300% of the measured I_{avg} depending on the application, and the patient's condition.

EEG-based Stimulation - Synchronization/Delay

[0030] To further improve the efficacy of a burst in terminating epileptiform activity, the subject invention also provides for synchronization of the burst with the EEG (Figure 6). To do this, a timing signal is generated off of the sensed EEG. A delay that varies from 0 to 100% of the detected EEG interval is initiated from the timing signal and is used to trigger the start of the burst. Graph 180 shows a representative EEG of epileptiform activity. Stimulation 182 shows a burst delivered with a 0% delay, that is simultaneous with a spike on the EEG. Stimulation 184 shows a representative burst having a 50% delay; and Stimulation 186 depicts a burst having a 75% delay. The synchronization technique described with regard to Figure 6 may be used in conjunction with the adaptive pulse-to-pulse interval as described in conjunction with Figures 5A to 5C in that a minimal number of pulses may be used in a burst, in some cases as few as one, but more typically three or four. By minimizing the number of pulses, a burst which is effective in terminating epileptiform activity is safer as it is less likely to provoke a seizure if accidentally applied.

[0031] A further method of synchronizing a burst is to trigger the first pulse of the burst selectively on a positive peak, a negative peak, or some other feature of the EEG signal. The detected EEG is preferentially from an electrode near or on the epileptogenic focus, but different features may be used to optimize the synchronization of the burst depending upon where the electrode is relative to the epileptogenic activity in the brain, and the patient's condition.

EEG-based Stimulation - Detection and Repetition

[0032] After the burst is delivered, the EEG is re-examined, and if the epileptiform activity was not terminated, a subsequent burst is delivered. The subsequent burst may have the same parameters as the first burst, may re-adapt to the changing EEG rate, or may have new parameters to more aggressively attempt to terminate the epileptiform activity (e.g. higher rate, more pulses, higher output, or modified pulse-to-pulse intervals).

Spatially-Determined Stimulation

[0033] One important aspect of this invention is the potential use of multiple brain contact electrodes to provide therapy. One embodiment of a device especially suitable for practicing certain variations of the inventive process is shown in Figure 7A. The Figure 7A includes multiple electrodes 701, 702, 703, and 704, to enhance the ability of

electrical stimulation to desynchronize brain activity to terminate epileptiform activity. Although the same burst may be delivered from a multiplicity of electrodes in the vicinity of the epileptogenic focus, it is preferable to provide bursts having different parameters, particularly pulse-to-pulse timing, to achieve a greater degree of spatial heterogeneity of neural activity and thereby most effectively desynchronize brain activity. This method for terminating epileptiform activity provides additional benefits in that lower current densities at the electrodes may be used to affect a larger amount of brain tissue than if a single electrode were used. Lower current densities are associated with fewer histological changes in the vicinity of the stimulating electrodes. Furthermore, the use of different burst parameters and/or lower current densities from a number of electrodes is less likely to initiate epileptiform activity or generalize on-going epileptiform activity.

[0034] Figure 7A depicts a representative electrode assembly placed under the dura mater on the brain, and viewed from above. There are four electrodes 701, 702, 703 and 704 in an insulated electrode backing 705 that prevents current flow back to the dura mater. Current flow back to the dura matter is often uncomfortable for the patient. The electrodes are electrically connected to the neurostimulator (not shown) by wires enclosed in the lead body 706. The epileptogenic region 707 is outlined for clarity, but is generally not visually apparent. To achieve spatial heterogeneity of electrical stimulation to most optimally desynchronize neuronal activity, the strategies described in this patent may be applied to all the electrodes 701-704 together or separately. Figures 7B, 7C, 7D, and 7E show an example of separate burst parameters being applied to electrodes 701, 702, 703 and 704 respectively to desynchronize neuronal activity in a wide area of brain tissue near the epileptogenic focus.

Implantable Neurostimulator

[0035] The inventive device includes a neurostimulator central unit and at least one electrode. The neurostimulator central unit includes the necessary circuitry, e.g., A/D converters, filters, central processing unit(s), digital processing circuits, blanking circuits, power supplies, batteries, signal generators, etc., and programming configured and adapted to perform the inventive steps listed above. Specifically the neurostimulator central unit (800) desirably is as shown in Figure 8 and is shaped in such a way that it conforms to the shape of the skull, although it need not be so. The neurostimulator central unit should at least contain an electrical stimulation source and preferably devices for detecting epileptiform activity and for initiating and for varying the responsive electrical stimulation as described above. The neurostimulator assembly should also include at least a first brain electrical activity sensor (802) and a responsive electrical neurostimulator electrode (804), preferably in the form shown in Figure 7A. The various necessary connectors, leads, and supporting components are also included.

[0036] A highly desirable aspect of the inventive device is the use of multiple brain electrodes to provide therapy. The measuring electrodes are preferable in contact with the brain, but, as discussed above, may be scalp electrodes or within the brain tissue. Multiple electrodes enhance the ability of electrical stimulation to desynchronize brain activity in terminating epileptiform activity. Although the same burst may be delivered from a multiplicity of electrodes in the vicinity of the epileptogenic focus, as noted above, preferable to introduce bursts having different signal parameters, particularly pulse-to-pulse timing, to the brain to achieve a greater degree of spatial heterogeneity of neural activity and most effectively desynchronize brain activity.

[0037] The application of multiple electrodes to different parts or regions of the brain also provide a way to treat epilepsy having more than one focus. Electrodes are placed on or near the various epileptogenic foci. The inventive neurostimulator may sense and stimulate independently from each electrode. Optional amplifier blanking eliminates cross talk, and logical flow in the device's software keeps the device from erroneously detecting its own output as epileptiform activity.

[0038] This inventive device may utilize independently actuatable, spatially separated electrodes so that those epilepsies having many epileptogenic foci or for which the focus is so diffuse the seizure arises from a large portion of the brain, may be treated. In such a case, it is desirable to place one electrode deep in the brain, preferably in the area of the hippocampus. Additional electrodes may be placed on the surface of the cortex. When epileptiform activity is detected, the device stimulates from the hippocampal region to take advantage of the large number of neural pathways emanating from that area into the cortex. Electrodes on the cortex provide additional electrical access to the brain allowing electrical stimulation to terminate epileptiform activity having a greater spatial extent.

[0039] Although preferred embodiments of the invention have been described herein, it will be recognized that a variety of changes and modifications can be made without departing from the spirit of the invention as found in the appended claims.

Claims

1. A method of setting a delay in initiating the application of at least one electrical burst to a brain, the method com-

prising determining the interval of an electrical signal in the brain prior to initiating the application of said at least one electrical burst and setting a delay in the initiation of the application of said at least one electrical burst after the onset of the detected electrical signal based on the interval of said electrical signal, the set delay period being between 5% and about 100% of said interval of said electrical signal.

5

2. A method as claimed in claim 1, wherein said electrical signal is an epileptiform electrical activity, said method further comprising the steps of again detecting said electrical signal in the brain after the application of said at least one electrical burst and analysing said electrical signal for epileptiform activity.

10

3. A method of determining when to apply to brain tissue at least one electrical burst comprising a multiplicity of pulses, said pulses having pulse parameters at least one of which will vary during the burst, the method comprising detecting an electrical signal in the brain representing epileptiform activity prior to initiating the application of said at least one electrical burst.

15

4. A method as claimed in claim 3, further including the step of determining the interval of said electrical signal in the brain prior to initiating the application of said at least one electrical burst.

5. A method as claimed in claim 4, wherein said at least one pulse parameter is related to said detected epileptiform pulse-to-pulse interval in the brain.

20

6. A method of determining when to apply to brain tissue at least one electrical burst comprising a multiplicity of pulses, said pulses having pulse parameters at least one of which will vary during the burst, the method comprising the steps of detecting an electrical signal in the brain representing epileptiform activity prior to initiating the application of said at least one electrical burst, determining the both the interval of said electrical signal in the brain prior to initiating the application of said at least one electrical burst and characteristic of the electrical signal, and delaying the initiation of the application of said at least one electrical burst after the onset of characteristic of the electrical signal for a period of time between 5% and about 100% of said interval of said electrical signal.

25

7. A method of determining when to apply to brain tissue at least one electrical burst comprising a multiplicity of pulses, said pulses having pulse parameters at least one of which will vary during the burst, the method comprising the steps of again detecting an electrical signal in the brain representing epileptiform electrical activity after the application of said at least one electrical burst and analysing said electrical signal for epileptiform activity.

30

8. An implantable neurostimulator assembly for treating a disorder in a human brain, comprising in combination:

35

a.) at least a first electrical neurostimulator electrode, and

b.) at least a first electrical signal source connectable to said at least first electrical neurostimulator electrode, said first electrical signal source initiating a stimulation burst to said at least a first electrical neurostimulation electrode, said burst comprising pulses having pulse parameters, which pulse parameters vary during said burst.

40

9. The implantable neurostimulator of claim 8 further comprising at least a first brain electrical activity sensor for sensing electrical activity in said brain.

45

10. The implantable neurostimulator of claim 8 wherein said first electrical signal source is configured to vary pulse parameters selected from the group consisting of electrode choice, pulse width, pulse amplitude, pulse polarity, and applied pulse-to-pulse interval.

11. The implantable neurostimulator of claim 8 wherein said first electrical signal source is configured to vary said pulse parameters randomly, pseudo-randomly, fractally, incrementally increasing, incrementally decreasing, or effectively to avoid initiation of epileptiform activity.

50

12. The implantable neurostimulator of claim 8 wherein said first electrical signal source is configured to deliver a hyper-polarizing pulse to said brain tissue prior to initiating the application of said at least one electrical burst.

55

13. The implantable neurostimulator of claim 12 wherein said hyper-polarizing pulse is 40 to 5000 microseconds in length.

14. The implantable neurostimulator of claim 12 wherein said hyper-polarizing pulse is comparatively lower in amplitude and longer in pulse length than pulses in said at least one electrical burst.
- 5 15. The implantable neurostimulator of claim 8 wherein said at least a first brain electrical activity sensor is configured to detect epileptiform activity prior to initiating the application of said at least one electrical burst.
16. The implantable neurostimulator of claim 8 wherein said at least a first brain electrical activity sensor is configured to determine the epileptiform pulse-to-pulse interval of said electrical signal in the brain prior to initiating the application of said at least one electrical burst.
- 10 17. The implantable neurostimulator of claim 16 wherein said first electrical signal source is configured to deliver an applied pulse-to-pulse interval that is varied in length between about 105% and about 400% of said epileptiform pulse-to-pulse interval.
- 15 18. The implantable neurostimulator of claim 16 wherein said first electrical signal source is configured to again apply to said brain tissue at least one electrical burst comprising a multiplicity of pulses, said pulses having pulse parameters, at least one of which pulse parameters vary during the burst, when said at least a first brain electrical activity sensor detects epileptiform electrical activity after application of said first electrical burst.
- 20 19. The implantable neurostimulator of claim 16 wherein said first electrical signal source is configured to vary said one or pulse parameters in said re-applied at least one electrical burst that are different than the pulse parameters varied in said at least one electrical burst.
- 25 20. The implantable neurostimulator of claim 8 wherein said first brain electrical activity sensor comprises multiple sensors.
- 30 21. The implantable neurostimulator of claim 20 wherein said multiple brain electrical activity sensors comprises sensors for measuring said at least one brain electrical activity of said brain simultaneously at different sites in said brain.
- 35 22. The implantable neurostimulator of claim 20 wherein said sensors are configured to measure said brain activity at a depth within the brain.
- 40 23. The implantable neurostimulator of claim 20 wherein said sensors are configured to measure said brain activity on the scalp.
- 45
- 50
- 55

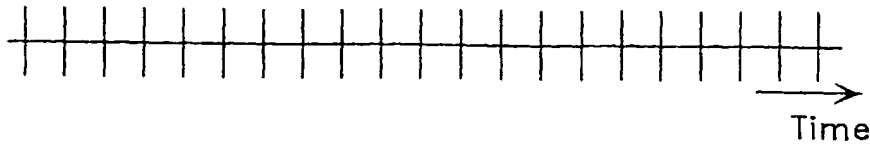


Fig. 1A

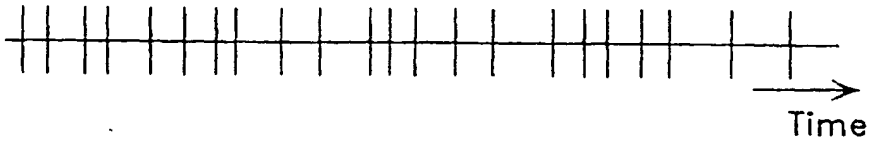


Fig. 1B

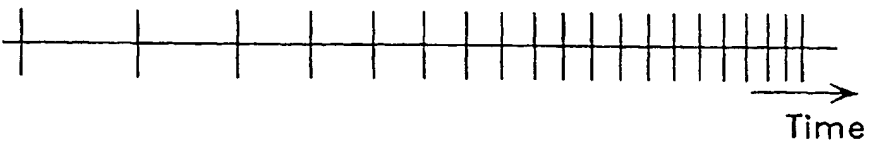


Fig. 1C

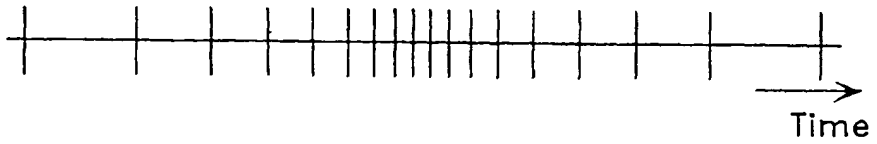


Fig. 1D

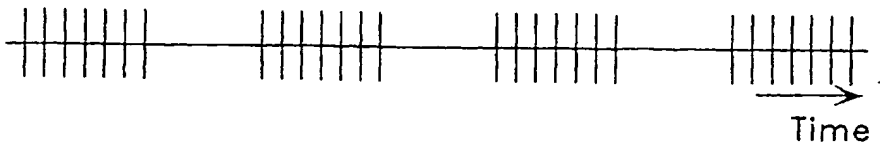
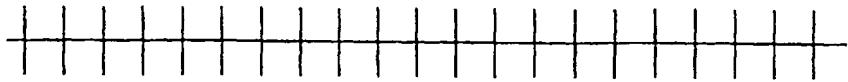
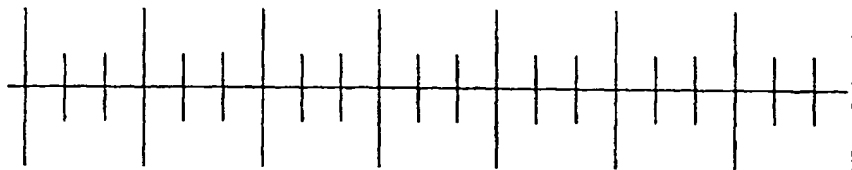


Fig. 1E



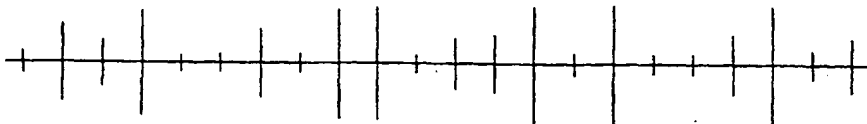
→
Time

Fig. 2A



→
Time

Fig. 2B



→
Time

Fig. 2C

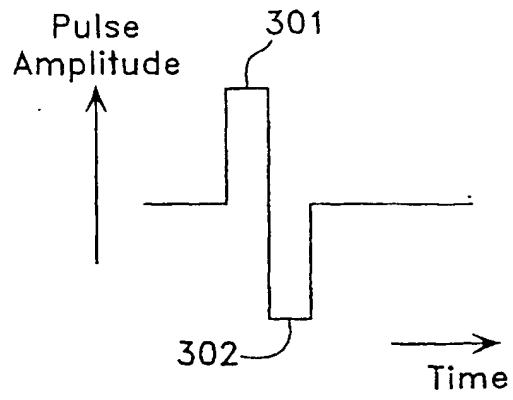


Fig. 3A

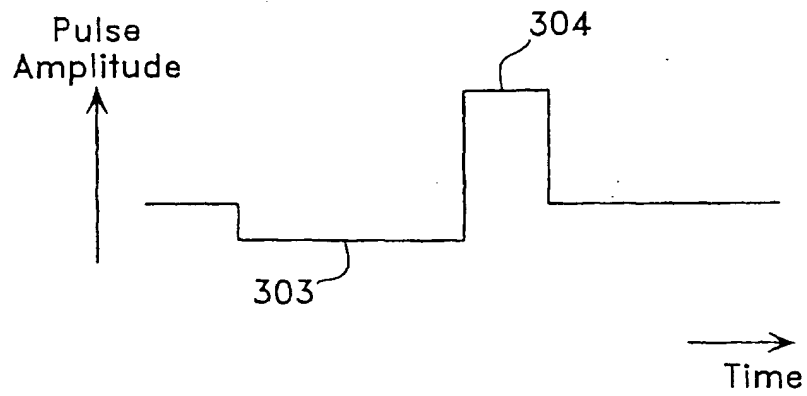
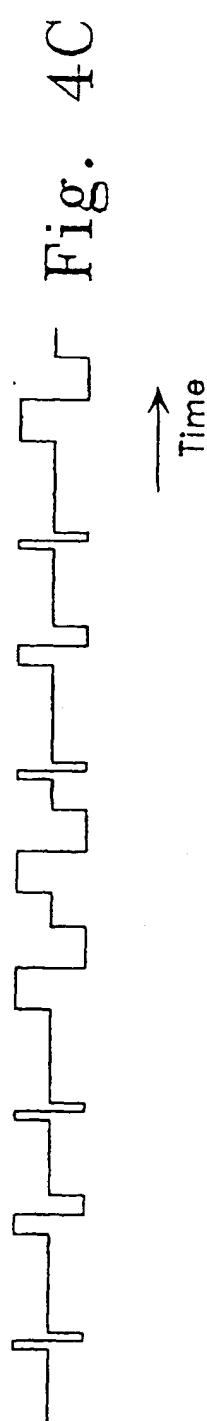
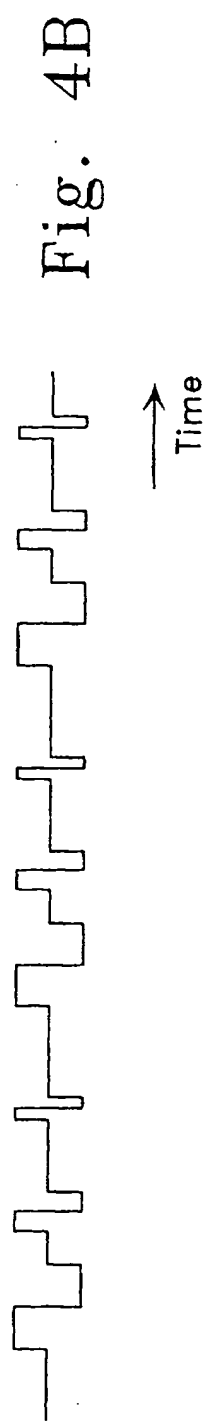
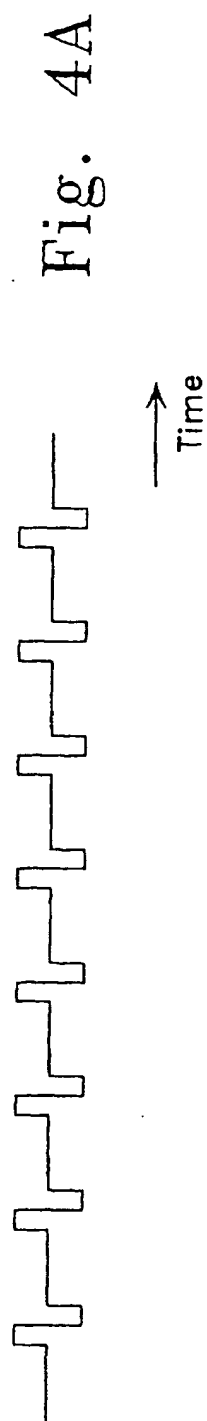


Fig. 3B



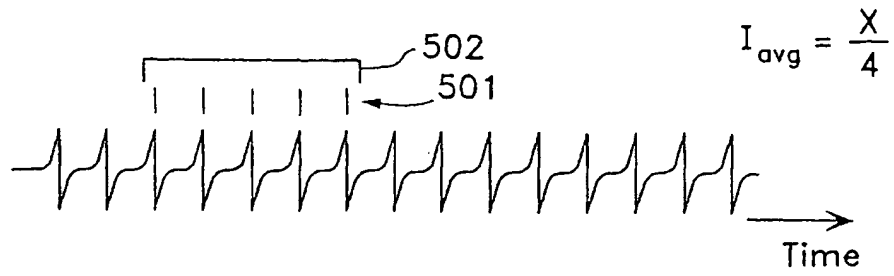


Fig. 5A

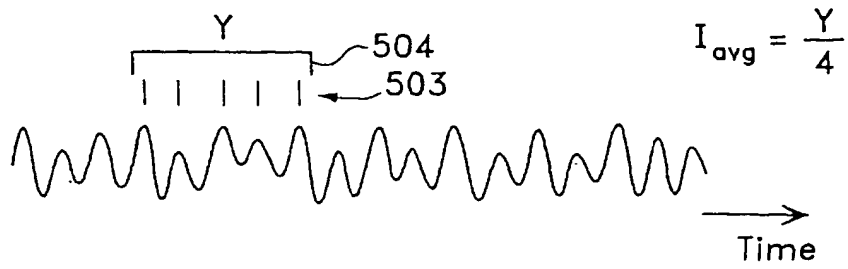


Fig. 5B

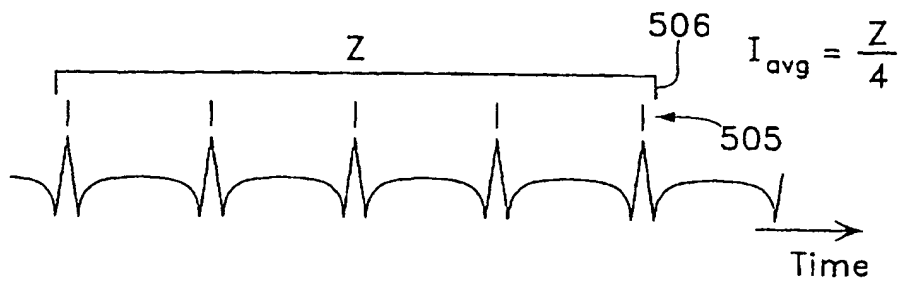
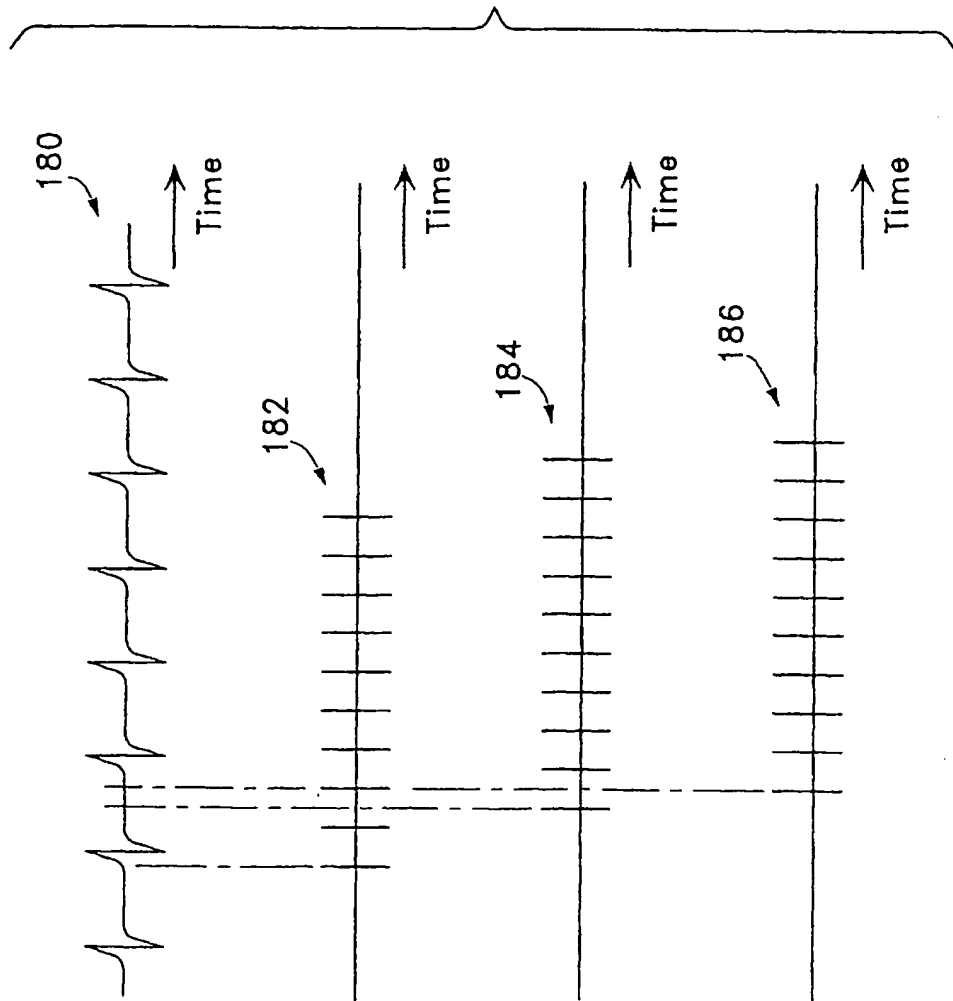


Fig. 5C

Fig. 6



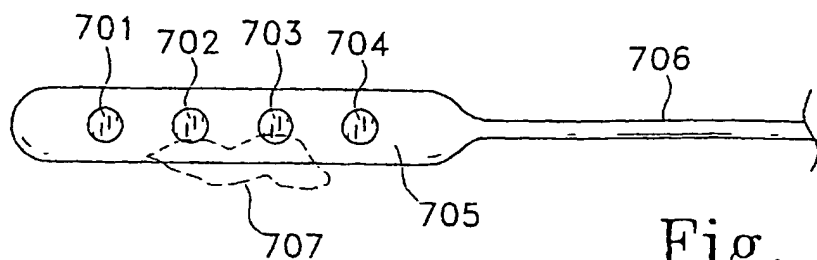


Fig. 7A

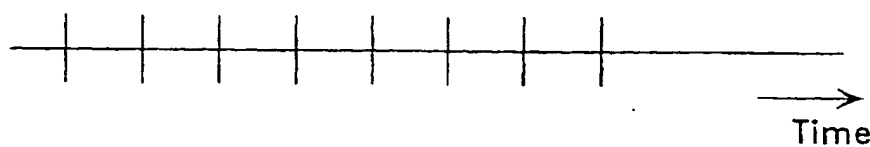


Fig. 7B

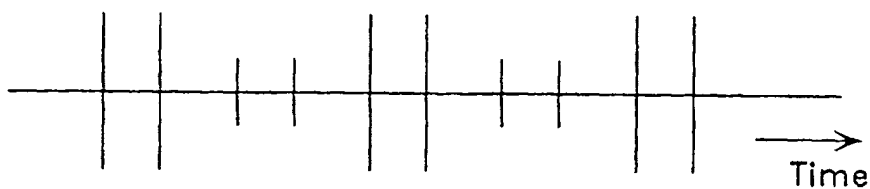


Fig. 7C

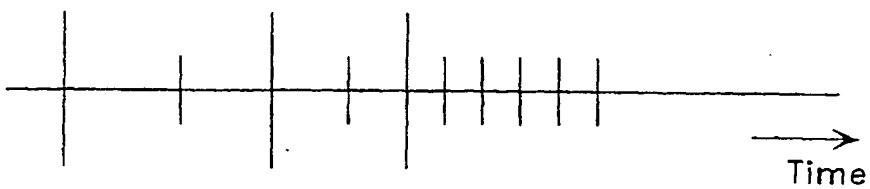


Fig. 7D

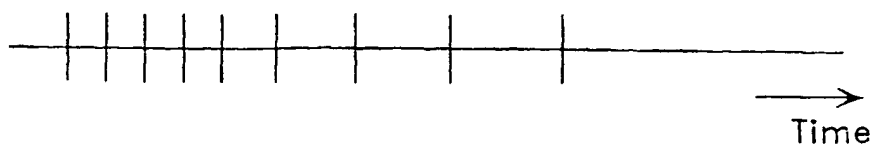


Fig. 7E

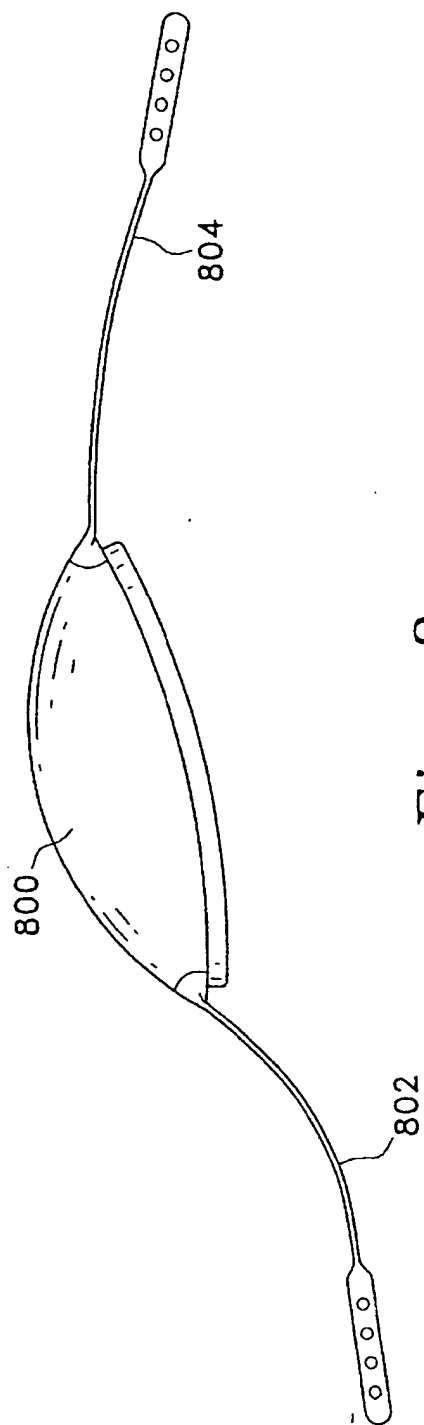


Fig. 8